HIV/AIDS

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The reason the POPS system works so well is that they have been revised many times based on feedback from students and faculty.
Please send suggestions and/or comments to: sleasjw@peds.ufl.edu

Note to Instructors
This workbook is divided into four sections:
(A) Introduction to the POPS System, introduction to and objectives of the clinical simulation, and a pretest
(B) Four booklets with pretest answers and the clinical problem(s)
(C) Posttest
(D) Posttest answers

Each student should receive a copy of section 1 to study and answer questions before the group problem-solving session. If you wish, section 2 also may be distributed for the students to review prior to the group session.

Introduction to the Patient-Oriented Problem-Solving (POPS) System

This is a Patient-Oriented Problem-Solving activity. The purposes are:

1. To help you learn how to apply your basic science knowledge to the solution of clinical problems
2. To help you learn how to better use sources (ie, textbooks and peers) that will be available to you throughout your career
3. To help you work with your fellow students and thus
   a. increase your ability to evaluate your colleagues' opinions, thought processes, and diagnoses
   b. increase communications skills
   c. get to know your classmates better

This activity consists of four phases.

- Before you come to class, you will review the attached set of objectives, do background reading on the topics to be covered, and complete the pretest on your own.
- In class, you will join three other students and review the pretest answers in an "open-book" discussion.
- The group will then solve patient-oriented problems. Information exchange and group interaction are keys to the success of this phase. This process will allow you to teach your fellow students and, at the same time, learn from them.
- Finally, you will take a posttest, individually, which will enable you to assess your progress and then review your answers with your groupmates.

HIV/AIDS

HIV infection and its late manifestation, AIDS, is a world-wide epidemic or pandemic, that is changing our world.

The goals of this activity are to:

1. Increase your knowledge of HIV infection, including methods to treat the infection.
2. Understand how molecular biology is applicable to clinical medicine.
3. Increase your awareness of some of the social and ethical issues related to HIV infection.

When you have completed this activity, you should be able to explain to another health professional or a lay person the following aspects of HIV infection:

a. How the virus is transmitted.
b. How HIV replicates.
c. How the immune system attempts to control HIV replication.
d. How HIV impairs the immune system.
e. The clinical signs and symptoms of HIV infection and AIDS
f. The rationale for HIV treatment.
g. Why a vaccine for HIV is so difficult to develop.

Please review the educational goals listed above and then take the pretest on the following pages. If you are uncertain about an answer, try to look it up. At the assigned time, you will meet with three of your classmates to discuss the pretest and work through the rest of the activity. The activity will be "open book" so be sure to bring your textbooks, articles, etc., to class.

As you ask the questions, practice using the "wait time" concept before calling on a groupmate. Research has shown that learning is increased 200-300% if one waits 3-5 seconds between asking a question and calling on someone. This enables everyone to formulate an answer and makes for much more active learning.

HIV/AIDS

Pretest

VIRAL LIFE CYCLE AND PATHOGENESIS

1. Order the following events so as to correspond to the sequence of events that occurs during HIV infection.

1. Viral DNA integrates into the host cell DNA.
2. The reverse transcriptase copies the viral RNA to produce a double stranded DNA.
3. The lymphocyte is "activated" and this induces the cell to copy viral RNA leading to translation into viral polyproteins.
4. Virus is packaged and polyproteins are cleaved into active proteins by proteases.
5. Virus induces cell death.
6. Virus gp120 attaches to CD4 and its chemokine co-receptor, gp41 leads to fusion between the lipid membranes of the virus and the cell.

(A) 1, 2, 3, 4, 5, 6
(B) 5, 4, 2, 1, 3, 6
(C) 6, 4, 5, 3, 2, 1
(D) 6, 4, 5, 2, 1, 3
(E) 6, 2, 1, 3, 4, 5

2. Match the HIV genes with their products or function.

(A) LTR	**1. p24**
(B) gag	**2. gp120, p41, gp160**
(C) pol	**3. reverse transcriptase, protease, integrase**
(D) env	**4. viral promoter function**
(E) tat, rev, vif, nef, vpr, vpu	**5. Regulation of viral replication**

3. Viruses that infect and replicate primarily in macrophages and CD4 T cells enter these cells using which of the following co-receptors.

(A) CD4 and CXCR4
(B) CD4 and CCR5
(C) CD4 and CD3
(D) CD8 and CD4

4. HIV leads to CD4+ T cell depletion by all of the following possible mechanisms except:

(A) Impaired production of new cells in the Thymus.
(B) CTL-mediated cell killing.
(C) Viral-induced apoptosis
(D) Viral lysis

5. Potential mechanisms by which HIV evades immune recognition and elimination include all of the following except:

(A) An error-prone reverse transcriptase leading to rapid viral evolution.
(B) Establishment of a latent infection
(C) Failure of antibody to effectively clear the virus.
(D) Lack of immunogenic viral epitopes.

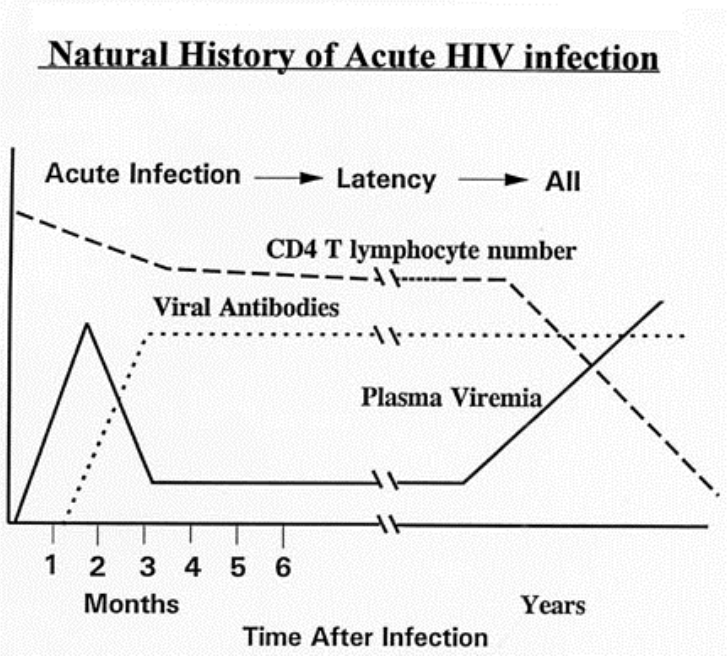
HIV INFECTION

6. The following graph depicts a common sequence of events following HIV-1 infection.

In the graph below, *CD4* refers to the level of CD4 T-cells in the blood, virus load refers to the level of HIV in plasma and antibodies (*anti-p24* and *anti-gp160),* refer to antibody to the HIV proteins, and CD4 T lymphocytes refers to blood levels of T helper cells.

Choose the number (1-6) on the graph which best corresponds to each of the descriptions below:

- Fever, swollen lymph nodes, weight loss, malaise.
- Seroconversion (ELISA/WESTERN blot positive)
- CTL response to control plasma viral load
- Rapid progression to AIDS, within two years
- Slow progression to AIDS, greater than five years.
- AIDS-defining illnesses (*e.g.* PCP, disseminated Mycobacterium infection, CMV retinitis, cryptosporidiosis)



7. Common ways that HIV is transmitted from an infected individual to another includes all of the following except:

(A) Unprotected sexual contact between an HIV-infected and uninfected individual
(B) Transmission from an infected mother to her child, either in utero or during delivery.
(C) Breast feeding from an infected mother to her child.
(D) Injection of illicit drugs.
(E) Blood donation.

ACUTE INFECTION

8. The acute phase of HIV infection involves all the following except.

(A) Viral infection of macrophages.
(B) Early high plasma viral levels.
(C) A latent reservoir of virus that is not responsive to treatment.
(D) Control of viral replication by cytotoxic T lymphcytes.
(E) Seeding of the virus to organs like the heart, brain, and lymphoid tissues.

9. Organ systems directly impacted by HIV infection includes all of the following except:

(A) CNS
(B) Lung
(C) Kidney
(D) Heart
(E) Musculoskeletal system

DIAGNOSIS AND TREATMENT

10. In regard to blood tests for HIV infection in adults, which one of the following is most accurate?

(A) ELISA and Western blot blood determine the amount of the virus in blood.
(B) A negative ELISA means the patient is not infected.
(C) A negative Western blot means the patient is not infected.
(D) A positive ELISA and Western blot in an adult means they are infected.
(E) A positive ELISA and Western Blot in a newborn means they are infected.

11. Match the following statement viral inhibitors with their action in the steps of the viral life cycle.

(A) Nucleoside reverse transcriptase inhibitors, e.g. AZT, ddI, 3TC.
(B) Non-nucleoside reverse transcriptase inhibitors (nevaripine, efavirenz).
(C) RANTES, Mip-1 α, Mip-1 β.
(D) Protease inhibitor.

1. Blocks viral binding to chemokine co-receptor.
2. Competes with cellular nucleotides to block production of viral DNA.
3. Binds to and inactivates reverse transcriptase.
4. Blocks cleavage of viral proteins.

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Pretest Correct Answers

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1. **The correct answer is - e.**

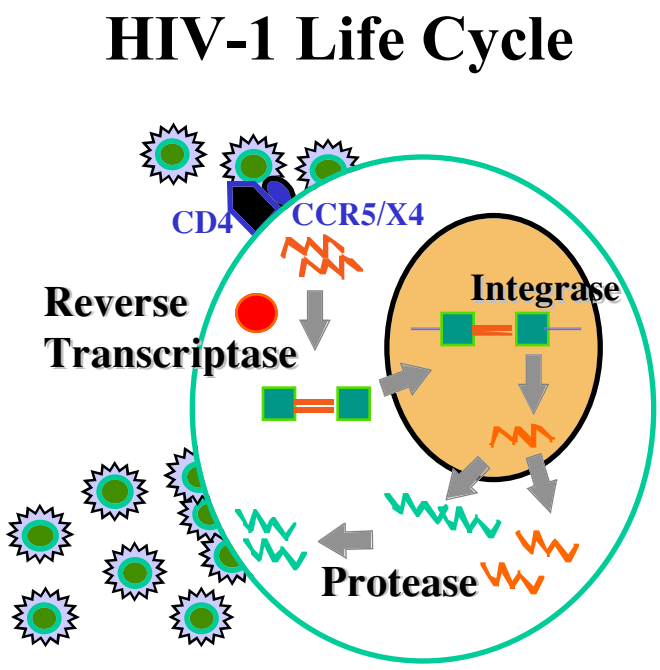

Figure 1

The steps of the HIV viral life cycle are summarized in Figure 1. The first step in HIV-infection is attachment of the virus to its receptor. The HIV envelope protein gp120 bonds directly to a molecule called CD4, a protein found on the surface of T helper lymphocytes and macrophages. (See Figure 2) CD4 is necessary but not sufficient for HIV entry into target cells. Interactions between gp120 and CD4 increases the affinity of gp120 for a second class of cell surface molecules, the chemokine receptors, which contribute to virus entry. Chemokine receptors are 7-transmembrane, G protein-coupled proteins that normally function in cell trafficking and response to inflammation. CCR5 and CXCR4 are two chemokine receptors that function as major co-receptors for HIV-1. (See Figure 2) CCR5 and CXCR4 are differentially expressed on distinct subsets of CD4-bearing cells and are critical

in determining viral tropism for primary T lymphocytes, macrophages, or transformed T cell lines. Tissues that use CCR5, which is expressed by macrophages and lymphocytes, are macrophage-tropic and most commonly found during acute and early infection. Viruses that use CXCR4, which is expressed by transformed T cells, can appear later in infection.

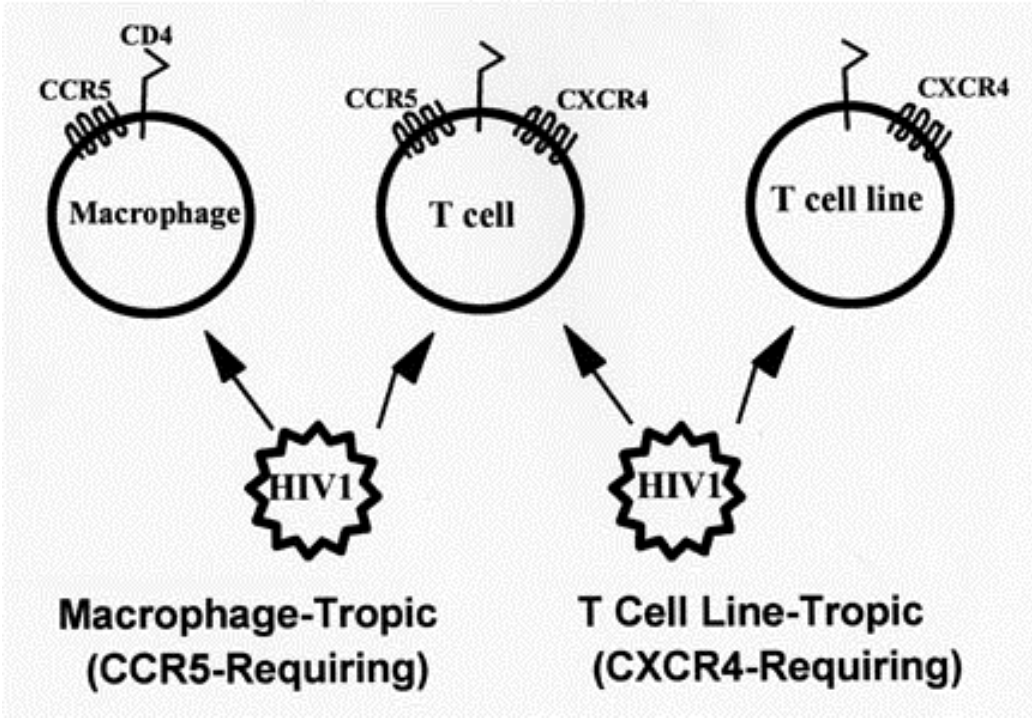

Figure 2

The second step is viral penetration. The lipid envelope of the virus, containing gp120 and gp41, fuses with the cell membrane, allowing viral entry. Within the cytoplasm viral RNA is copied into double stranded DNA by a unique retrovirus enzyme, reverse transcriptase. The viral DNA is transported into the nucleus of the cell and is poised for the next step in the viral life cycle, integration.

The viral encoded integrase enzyme catalyzes integration of viral DNA by a covalent linkage to the host cell's chromosomal DNA, resulting in HIV-1 DNA becoming an actual component of the host cell genome. Viral expression results in transcription of proviral DNA into viral mRNA, which is dependent upon host cell activation and host cell enzymes. T cell activation activates provirus expression through the target sequences in the LTR. The full-length RNA transcripts are spliced and transported to the cytoplasm where HIV-1 RNA is then translated into viral proteins by normal cellular mechanisms. The regulatory gene products, tat and rev, are thought to play a key role in this phase of the viral life cycle. Viral proteins are processed, assembled into new viral particles, and bud from the surface of the HIV infected cell.

(F) **The correct answer is - e.** HIV infection can be transmitted in many ways. The most common mechanism of transmission is through unprotected sexual contact with exchange of bodily secretions from an infected individual to an uninfected individual. Transmission can result through either anal, vaginal, or penile routes. Viral transmission can also occur through receptive oral intercourse, however exposure to oral secretions such as occurs through kissing or other types of exposure to oral mucosal secretions is a very rare mode of transmission.

Other routes of infection include transmission through infected blood or blood products. Such routes of infection would include infection through blood transfusion, recipients of HIV-infected organs or

tissues through transplantation, and individuals who have received clotting factors for the correction of hemophilia or other coagulation disorders. Health workers exposed through needle sticks or similar accidents with HIV-infected patients can become infected. Intravenous drug users who share needles with infected individuals can also become infected. HIV can be transmitted from mother to child. HIV can be transmitted in-utero, during labor and delivery, or through breast feeding. HIV infection is not transmitted through blood donation assuming that sterile needles are being used to collect the blood samples. There is no evidence that HIV is transmitted through incidental exposure to infected secretions, by biting insects, or by aerosol.

Patient I: Gertrude Grauidstein

Gertrude is a 25 year old woman whom you are seeing in your office for the first time. Gertrude is in the fourteenth week of gestation as the result of a planned pregnancy. She received voluntary HIV testing as part of the routine evaluation of her pregnancy. She has not previously been tested for HIV. The ELISA is positive.

What would you do?

1. What should be the next series of laboratory studies you should do to evaluate Gertrude's condition.

   The most prudent course in the management of Gertrude and her baby would be to repeat the HIV ELISA and Western Blot.

2. The results of both tests are positive. What now?

   A careful history and physical exam should be done to detect the clinical signs and symptoms of HIV infection. T cell subset analysis and HIV plasma viral load should be done for clinical staging.

3. What should Gertrude tell her husband?

   What Gertrude should tell her husband is a difficult situation. Her husband's reaction could put her at risk to become a victim of domestic violence. It is possible that Gertrude obtained HIV infection as a result of infection from her husband or that she could have obtained HIV infection from another sexual partner. Infection could have occurred years ago and she may have harbored the virus in her body even before she was married. You should explain to Gertrude all of these possibilities. Regardless of the circumstances, Gertrude's husband should be tested for HIV infection. If he is negative they should use a barrier method for contraception. If he is positive then he should be evaluated and treated for his infection. Some states require HIV reporting of infected individuals to local health departments and partner notifications are carried by the public health team. It is your responsibility to know your state laws.

4. How would you advise Gertrude about her pregnancy? What is the probability that her baby will be infected?

   Not all infants born to HIV pregnant mothers become infected. Without antiretroviral therapy to prevent maternal transmission, perinatal infection in the United States is approximately 30%. The use of antiretroviral medications during pregnancy, labor, and antiretroviral medications administered to the baby for the first six weeks of life reduces the chance of transmission to less than 5%. It is imperative that Gertrude receive antiretroviral therapy both for her own health as well as for the health of her infant. Some women choose to have a therapeutic abortion.

5. How will you determine if her baby is infected?

Because maternal IgG antibody crosses the placenta all babies born to HIV infected mothers will test positive by the ELISA and Western Blot assays. Therefore, these laboratory studies are not an effective ways to screen for HIV-infection in infants. The best test for HIV-infected infants detects the presence of the virus itself. These studies include the HIV PCR assay which detects proviral DNA, the HIV RT-PCR assay which detects free virus in the plasma, and HIV viral culture which is not as sensitive as the other two tests. The current recommendation for testing HIV exposed infants is to determine the presence of the virus using the DNA PCR assay. This assay should be performed at birth, 2 months, and 4 months. If all of these tests are negative then there is a >95% chance the baby is not infected. The definitive test is to observe the seroreversion from an HIV antibody positive status to an HIV negative antibody status between 12 and 18 months of age.

6. How would you treat Gertrude's baby?

As above, Gertrude, should receive antiretroviral therapy after birth, Gertrude's baby should be treated for approximately 6 weeks with antiretroviral therapy to prevent infection of her baby. Gertrude should be advised not to breast feed her infant as human milk carries the HIV virus and there have been reports of transmission through breast milk. Gertrude's infant needs close medical follow-up to confirm either HIV-infection or document sero reversion to an HIV negative state. The current recommendations for all infants who are at risk for developing HIV infection is that they should receive prophylaxis for Pneumocystis carinii pneumonia for the first year of life. Finally, Gertrude's baby should receive routine immunizations but should not receive immunizations which contain live viruses such as polio, varicella (chicken pox), and the measles, mumps and rubella vaccine until the status of the infant is known. This is because children who are immunocompromised who receive live immunizations can develop those diseases.

Ethical Issues/Attitudes

Should there be mandatory HIV testing for all pregnant women in the United States?

Objectively discuss the advantages and disadvantages of this proposal. Are there compromises to mandatory testing that might achieve the objective of the identification of mothers who are at risk for HIV vertical transmission?

Pros

Testing would facilitate the early identification of HIV infected women during pregnancy and enable them to receive treatment with antiretroviral medications to prevent infection of their infants. This strategy has been shown to be effective in reducing maternal transmission and could prevent AIDS in thousands of infants who are at risk for HIV infection each year.

Because many HIV infected women are asymptomatic and do not know that they harbor HIV virus testing would allow them to receive early antiretroviral treatment to improve their own health.

If a woman knows her HIV status then education could be implemented which would prevent further transmission of the virus to others and reduce the spread of HIV infection through sexual contact.

Mandatory screening of pregnant women for syphilis has been in place for many years and has been shown to be effective in preventing neonatal syphilis.

Cons:

Less than 1% of all pregnant women are infected by HIV. Therefore, 99% or more of woman who receive this screening will not need it. This may not be cost effective.

Mandatory HIV screening is an unnecessary infringement of a patient's rights to choose her own medical care.

Mandatory screening could result in the loss of confidentiality in those women who are identified as being HIV positive.

Some women might avoid prenatal care in order to avoid HIV testing.

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Answer to question 2:

a.	*LTR*	4.	viral promoter function
b.	*gag*	1.	p24
c.	*pol*	3.	reverse transcription, protease, integrase
d.	*env*	2.	gp120, gp41, gp160
e.	*tat, rev, vif, nef, vpr, vpu*	5.	Regulation of viral replication

Genetic Organization of HIV-1

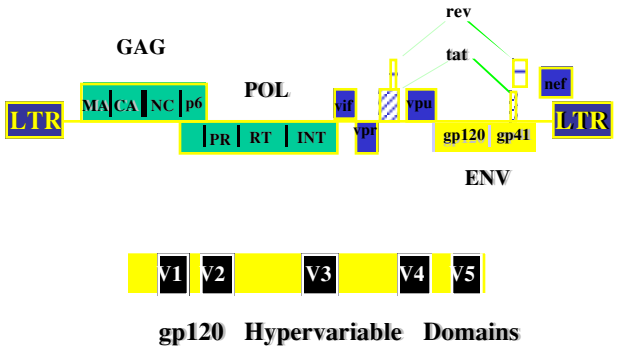

Figure 3

The proteins and enzymes involved in the structure and replication of HIV are encoded by a linear viral genome, which is organized into three major genes: *gag*, *pol*, and *env* (See Figure 3). These genes are transcribed into RNA and ultimately translated into viral proteins that are generally identified by their molecular size. For example, **p24** refers to the 24-kDa core protein encoded by *gag*, whereas **gp120** refers to a 120-kDa glycoprotein located in the viral envelope. *Gag* is a major gene encoded by the HIV-1 core proteins. *Pol* encodes at least three enzymatic activities: **protease**, (PR), an enzyme involved in the cleavage of the *gag* and *pol* encoded protein precursors; **reverse transcriptase**, (RT), essential for transcribing the RNA genome into DNA; and **integrase**, (INT), required for the covalent linkage between the viral DNA and the host cell chromosome DNA. *Env* encodes gp160 a glycoprotein that is processed into gp41 and gp120. The smaller gp41 spans the lipid envelope membrane and serves as the anchor for gp120 which interacts with receptors on the surface of target cells. In addition to *gag,*

pol, and *env,* the HIV genome contains a set of regulatory genes that are involved in positive and negative modulation of virus replication. The regulatory genes include *Tat*, a potent transactivator of HIV gene expression that facilitates the initiation of RNA transcription; *Rev*, which facilitates the transport of unspliced RNA from the nucleus to the cytoplasm; and the regulatory and accessory genes which include *Nef, Vpr, Vpu*, and *Vif*. The **regulatory genes** which overlap *pol* and *env* and are expressed by complex splicing mechanisms are unique to the lentiviruses such as HIV. Flanking the coding regions of the HIV genome are long terminal repeats (LTRs) composed of sequences that carry **promoter function** and thus regulate virtually every aspect of the virus lifecycle. This includes replication, integration, and viral gene expression.

The correct answer to question 8 is - c. HIV gains entry into mucosal surfaces by binding first to local dendritic cells and tissue macrophages along the mucosal surface. Following this event, CD4 T cells interact with macrophages and become activated. These cells set up a local infection and there is migration of infected cells to regional lymph nodes. Within regional lymph nodes, viral replication increases dramatically and there is a phase of viremia within seven to fourteen days following initial exposure. During viremia there is seeding to all lymph node tissues as well as to other organs that are affected by HIV including brain, kidney, lung and heart. During the initial phase of viremia, cytotoxic CD8 positive T lymphocytes recognize viral antigens on infected cells and destroy them. Infected cells also die through a process called apoptosis. The dynamic between production of new virions by infected cells and clearance of infected cells and virus by antibody and cytotoxic T lymphocytes result in a steady state set point of viremia. The set point is also influenced by the number of infected cells that are producing cells. Long lived cells and phenoritic cells which harbor virus contribute a small proportion of free virus (25%). Infected CD4 T cell contributes > 95% of free virus. The half life of a free virion is about 6 hours. The half life of an infected CD4 T cell before it dies either due to CTL mediated lysis or apoptosis is about 1.3 days. The relative level of free virus within the blood predicts the rapidity of progression to AIDS.

The correct answer to question 9 is - e. HIV impacts multiple organs systems. HIV is thought to enter the brain through HIV infected macrophages that result in an inflammatory response with destruction and apoptosis of neural cells. The pathologic manifestation of this process is a progressive, diffuse, chronic encephalopathy characterized by loss of myelin in the deep white matter and the formation of multinucleated giant cells. HIV-infection is becoming one of the most common forms of chronic encephalitis/encephalopathy in the world. HIV infection also causes a chronic pneumonitis, especially in children, through infection of lung macrophages. It is the common cause of proteinuria and kidney failure in infected individuals. Finally, HIV causes a dilated cardiomyopathy. It has minimal direct effect on the musculoskeletal system.

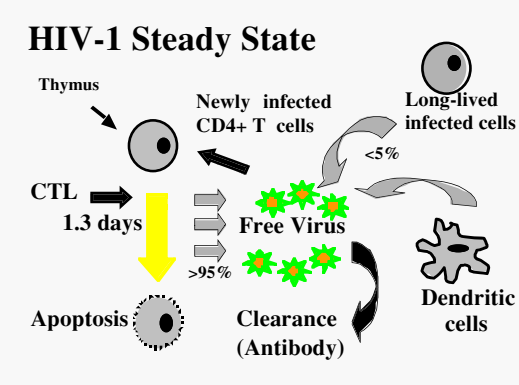

Figure 4

Patient II: Fred Friendly

Fred is a 35 year old, white male, advertising executive, comes to the clinic with a four day history of fever, malaise, swollen lymph glands and ten pound weight loss. He has a history of several episodes of unprotected sexual encounters. His physical examination reveals oral *candidiasis* and axillary and cervical adenopathy.

What would you do?

1. What are conditions that could explain Fred's symptoms?

   There are several conditions that could explain Fred's symptoms. These include Epstein-Barr (EBV) virus infection (mononucleosis), cytomegalovirus (CMV) infection, or other viruses or bacteria which cause swollen lymph glands and fever. Because of the poor prognosis and the high degree of sexual transmission associated with HIV infection, HIV must be considered. Candidiasis (Thrush) would be very unusual in any condition except HIV infection.

2. What laboratory tests could you do to confirm your diagnosis?

   Laboratory tests that could help you in making Fred's diagnosis of his acute illness include serologic evaluations for EBV, CMV and other viral pathogens. The best HIV screening test would be an HIV ELISA. However, because Fred may be in the acute phases of his HIV infection it is possible that the HIV ELISA and Western Blot will be negative even though he is HIV infected.

3. Fred doesn't remember ever being tested for HIV. He is a regular blood donor and is scheduled to give blood next week. What would you advise?

   Any patient who has fever, or signs and symptoms of an acute infectious illness should not be a blood donor. You should advise Fred not to donate blood donor because he is in a high-risk group for CMV and HIV infection and therefore his blood could transmit infections to others.

1. Fred calls your office back in two weeks to say that he is feeling somewhat better, has no fever, but has not yet regained all of his weight. What would you do at this point?

   You should plan to see Fred back in your office after his acute illness. This is common medical practice for patients who have illnesses for which there is no obvious diagnosis during the acute phase of their infection. At this point you should consider doing a repeat HIV ELISA and Western Blot.

2. Fred's ELISA and Western Blot are positive. You perform an HIV plasma viral load which is 135,000 HIV RNA copies per microliter of plasma.

   Fred has confirmed HIV-infection with an elevated viral load. The best medical care for Fred would be to evaluate his T cell subset, obtain a complete CBC with differential, evaluate his liver and renal function, and consider an MRI of his brain if he has evidence of neurological symptoms.

Approximately 40 to 60% of patients with acute retroviral syndrome will have neurological symptoms that may range from simple headache to meningoencephalits. It has been shown that treatment of acute HIV infection with combination antiretroval therapy may lower the viral set point and delay progression to AIDS. You should discuss the relative risks of treatment with combination antiretroviral therapy compared to their potential benefits with Fred. You should also advise him that even with treatment he is potentially infectious and he should use a barrier method for contraception for all future sexual encounters.

3. Fred tells you that he is married and does not want his wife to know about his HIV status. He also does not want to use a condom with his wife because it would make her suspicious. How would you advise Fred about this issue?

   Fred should know that in most states it is a felony to knowingly expose someone else to possible HIV infection. Fred needs to discuss his diagnosis with his wife, use barrier contraception, or abstain from having sexual relations with his wife.

Ethical Issues/Attitudes

Many states are starting programs of name reporting and mandatory partner notification for HIV infection to public health officials. Should it be mandatory that all HIV infected individuals be reported to their local county health department and that their sexual partners be notified of their risk for HIV infection?

Objectively discuss the advantages and disadvantages of this issue. Weigh the pros and cons of these types of policies.

Pros:

Education is an effective way to reduce the HIV epidemic. If partner notification were implemented then infected individuals would know their status and could use barrier forms of contraception to prevent transmission. Education and changes in sexual behavior strategy has been shown to be highly effective in reducing the number of new cases of HIV infection.

The early identification and initiation of treatment with antiretroval therapy delays progression to AIDS. In this way HIV positive individuals could receive early therapy that would benefit their health.

Mandatory reporting would allow the public health service to track the HIV epidemic in this country. They would know the number of HIV infected individual and not just the number of individuals who have AIDS, the end stage of HIV infection.

Case tracking and notification of other individuals at risk for infection with transmissible infections has been effective in controlling the spread of other infectious diseases such as syphilis and tuberculosis.

Cons:

Partner notification is a breach of patient confidentiality and an infringement of individual patient rights.

Mandatory HIV name reporting and partner notification may actually decrease the number of individuals who are tested and cause people to delay their receiving treatment.

If asymptomatic people are treated for HIV infection they will live longer, require long term therapy with expensive medications and will be likely to raise the overall cost of health care.

HIV/AIDS

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Note to Students

The fundamental purpose of all activities in health-care professions is to help other people. Like all behavior, helping behavior becomes more effective and natural with practice. This workbook enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future.

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BOOKLET C

Pretest Correct Answers

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The answer to question 3 is - b. CD4 is necessary for HIV entry into target cells, but a chemokine co-receptor is also required. (Figure 2) Chemokine co-receptors consist primarily of the CCR5 co-receptor expressed on macrophages and T cells and the CXCR4 co-receptor that is expressed on T cells as well as other cells of the body. Viruses that replicate primarily in macrophages utilize the CCR5 co-receptor whereas viruses that proliferate primarily in T cells utilize the CXCR4 co-receptor. Binding of viral gp 120 to its co-receptor can be inhibited by the natural ligands for chemokine receptors, soluble factors such as RANTES, MIP-1α, and MIP-1β, which compete for HIV gp 120 for receptor binding.

The answer to question 5 is – d. HIV-1 demonstrates extensive variability among its genome. Errors introduced by HIV-1 reverse transcriptase occurs as frequently as one in ten thousand nucleotides. This error rate can produce at least one genetic change during each viral replication cycle. In addition to nucleotide substitutions, nucleic acids can be deleted or new nucleic acids can be inserted within the HIV genome. The resulting deletions, insertions, and/or duplications that occur during the process of reverse transcription leads to a high degree of genetic variability within the HIV-1 genome, so that an infected individual has 10^6-10^9 genetically distinct viruses. The extent of genetic variability among different strains of HIV-1 has important implications for tracking the epidemiology of HIV-1 and also can be used to track viruses transmitted from one person to another.

Although nucleotide changes can occur within the viral genome, the extent of genetic variability is not uniform within the various gene segments. Conserved regions of gag and pol display less variability than env presumably because the function of proteins encoded by *gag* and *pol* need to be conserved in order to maintain enzymatic activity. In contrast, the most variable regions of the various genomes are centered in the five hypervariable regions in gp 120, a finding that suggests that changes within these regions are driven by the immune response. Selective pressure by the immune system leads to viruses that have different envelopes that allow them evade cellular and antibody immune responses. A similar

phenomenon is seen when patients are treated with combination antiretroviral therapy. New mutations evolve very quickly resulting in emergence of drug resistance strains.

Consequently, the answer is d because HIV induces antibody against its viral epitopes.

The answer to question 11 is: a – 2; b – 3; c – 1; d – 4. The current therapeutic strategies to suppress viral replication in infected individuals uses antiretroviral agents that act at distinct stages of the viral life cycle(See Figure 6). The dideoxynucleoside reverse transcriptase inhibitors, (NRTI's), such as zidovudine (also known as AZT), act on the infection phase of the virus life cycle by competing with endogenous deoxynucleotides for incorporation into viral DNA during reverse transcription (RT), from viral RNA. Once the drug is incorporated into viral DNA further elongation of the DNA chain is terminated. In addition to zidovudine and related analogues, there are several non-deoxynucleoside analogues that inhibit the infective process of the virus life cycle but have no activity against the phase of viral replication. Non-nucleoside reverse transcriptase inhibitors, (Non-NRTI), such as nevaripine, efavirez and delavirdine, bind directly to reverse transcriptase to inhibit its function.
The HIV protease is a unique enzyme that is responsible for the cleavage of the large *gag* and *pol* precursor proteins, and is an essential requirement for the production of infectious virus. Protease inhibitors compete with the substrate by binding to enzymatic active site. This results in incomplete

Sites of action of antiretroviral therapy in the HIV Life Cycle

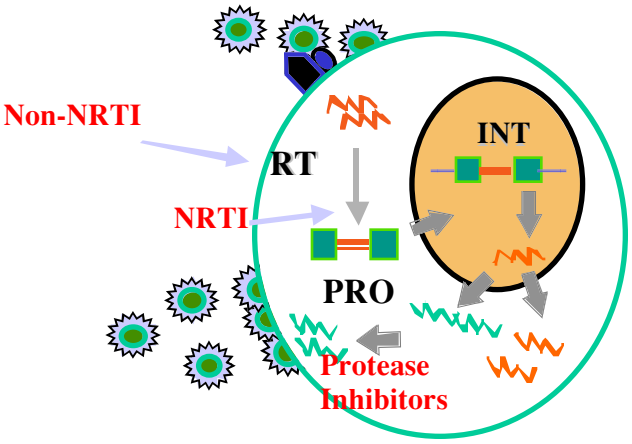

Figure 6

processing of the polyprotein precursor into structural proteins and enzymes, and ultimately in the production of non-infectious virions. All anti-retroviral agents are hampered by the emergence of therapy resistant viruses. In addition, RANTES, Mip1α, Mip1β blocks HIV binding to CCR5 and CXCR4. These are "natural" inhibitors to viral replication.

Patient III: Ted Trackman

Ted is an HIV positive intravenous drug user who comes to your outpatient clinic with a persistent, severe cough and breathing problems. He had been treated with AZT monotherapy four years ago, but was then lost to follow-up until now. His CD4 count is less than 50 cells/microliter, and his viral load is 150,000/microliter.

1. What tests would you order?

Because Ted has extremely low CD4 count he is a risk for developing a number of opportunistic infections. These would include the possibility of pneumonia, tuberculosis, Mycobacterium avium infection, CMV, or other opportunistic infections of the lungs. Because of the broad range of pathogens that could account for Ted's cough, fever and breathing problems the first thing to do would be a chest x-ray. A chest x-ray would help you to determine what type of pneumonia could be the cause of Fred's symptoms. Doing a broncho alveolar lavage could make the definitive diagnosis. Using the specimen obtained directly from the lungs, a definite diagnosis can be made and allow you to initiate appropriate therapy for the underlying pneumonia.

2. His pneumonia is due to *Pneumocystis carinii pneumonia*. What therapy would you recommend?

The best treatment for pneumocystis carinii pneumonia, (PCP), is the use of trimethoprin sulfamethoxazole, (TMP/SMX). In addition to treating his underlying pneumonia, Ted needs to be treated with combination antiretroviral therapy to control his HIV. PCP can also be prevented using TPM/SM2 prophylaxis. Ted has AIDS and without treatment he is likely to die within the next year.

3. How would you treat advanced (and probably AZT-resistant) HIV?

Ted needs to know that treatment for HIV infection requires strict adherence to a difficult medication regimen. Patients sometimes have to take between 8 to 10 different medications and up to 50 pills per day in order to control their virus and prevent further opportunistic infection. Many of these medications have toxic side effects and there is no guarantee, even if Ted is compliant with his medications, that he can restore his immune system and control his virus. Ted should be treated with nucleotide reverse transcriptase inhibitors plus a protease inhibitor, and NNRTI, to control viral replication. In addition he will need ongoing therapy for PCP and prophylaxis to prevent other opportunistic infections. If Ted cannot strictly adhere to this medication protocol it is likely that his virus will continue to replicate and will also be resistant to the medications he was receiving. There is growing emergence of drug resistant strains of HIV in the United States. For this reason many physicians do not treat patients whom they think will not have good compliance with potent antiretroviral agents such as protease inhibitors.

Ethical Issues/Attitudes

Many HIV physicians will not prescribe potent highly active antiretoviral therapy to patients who they know will not adhere to their medication regimen. The reasons for this are several:

1. Individuals who do not strictly adhere to their medication schedule are likely to have viral break through and the viruses that emerge under the selective pressure of combination antiretroviral therapy are highly likely to carry mutations which will confer resistance to the medications they are receiving as well as cross-resistance to other antiretroviral agents. For this reason it will be more difficult to control their viral replication in spite of the use of combination antiretroviral therapy.

2. It is likely that the emergence of drug resistant variand of HIV will be transmitted into the general population through sexual contact. As a result, individuals may be infected with resistant viruses thus making it more difficult to treat HIV infection within the population. Discuss the ethical implications for withholding therapy from a patient such as Ted.

Question: Should physicians not prescribe combination antiretroviral therapy to patients who they think will not be compliant with their medications?

Pros:

Highly active antiretroviral therapy is extremely expensive and the funds to pay for these therapies often comes from state and federally sponsored programs that are funded through tax dollars. These precious resources should not be used for individuals who are unwilling or unable to use these medications.

The improper use of highly active antiretroviral therapy only leads to the emergence of resistance viruses and in the long run may actually harm the patient. These agents should be reserved for those individuals who can adhere to their treatment regimen even if that means they will get progressively ill without proper therapy.

The improper use of highly active antiretroviral therapy will lead to the emergence of resistant viruses throughout the country. This will lead to an increase in the HIV epidemic and will ultimately result in more people getting AIDS. The emergence of resistant tuberculosis has already had a dramatic impact on the tuberculosis epidemic in this country as well as other countries.

Cons:

It is a physician's reponsibility to prescribe the best possible therapy for their patient. Physicians should not be in a position to judge who may or may not take any given medication.

Even some therapy is better than no therapy. There is some evidence that the viruses that emerge under the selective pressure of antiretroviral therapy may have less pathogenic potential that wild type viruses.

It is much more cost effective to treat individuals before they develop AIDS than it is to treat the complications of AIDS, therefore, any treatment strategy that will delay progression to AIDS may ultimately be more cost effective.

New treatments are constantly being developed for treatment of HIV infected individuals. Resistance is a natural occurrence and therefore physicians should not be concerned about the development of mutations that confer resistance to certain strains of the HIV virus.

HIV/AIDS

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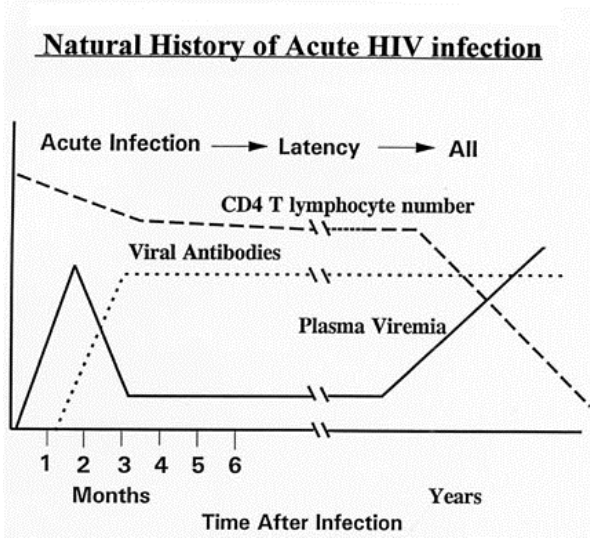
The correct answer to question 4 is - d. HIV leads to CD4 T cell depletion by multiple mechanisms. First, HIV can infect the thymus resulting in impaired thymic production thus lowering the number of mature T cells that leave the thymus. In addition, cytotoxic CD8 positive T cells recognize infected CD4 cells and destroy them. Finally, HIV alone can induce apoptosis of infected cells. HIV buds from cell surface and as such is not a highly lytic virus. Direct viral lysis plays a minor role in depletion of CD4 T cells.

Answer to question 6. The events during primary infection following sexual contact are characterized by the following events.

Infection of local tissue macrophages, dendritic cells, and CD4 T lymphocytes.
Viral replication in regional lymph nodes.
Viremia and dissemination of virus to all lymphoid tissues.
Immune recognition, first by CD8+ cytotoxic T lymphocytes, reduction of viral load, and production of anti-HIV antibody.
Establishment of viral steady state (set point).

Natural history of HIV-1 infection. After initial infection there is an acute phase of plasma viremia as represented by the solid line on this figure. Acute viremia peaks 4 –12 weeks after exposure but falls soon after the appearance of HIV viral antibodies, as represented by the dotted dash line. During this phase of acute infection, or acute retroviral syndrome, infected individuals experience a "mononucleosis" type illness with malaise, fever, night sweats, anorexia, headaches, rash, swollen lymph glands, and splenomegaly. Some individuals become quite ill while others only report a mild "flu-like" illness. Following the acute illness most patients go into a phase of clinical latency in which they are relatively asymptomatic. HIV antibodies remain detectable throughout the course of infection. During the acute phase of infection there is evidence of T-cell activation and an increase in the number of circulating CD8 T cells as evidenced by an inverted CD4 to CD8 ratio. This inverted CD4 to CD8 ratio persists during clinical latency. Cytotoxic T lymphocytes, (CTL), targeted against HIV antigens control plasma virus levels by destroying infected cells, i.e., the virus factories. Control

of viral replication by the combination of anti-HIV antibodies and CTL response is the principal determinant of the viral set point or level of "steady state" plasma viral levels during latency. Patients who have high numbers demonstrate a rapid fall in CD4 count and progress to AIDS within two years. Patients with low numbers progress to AIDS over a longer period of time. AIDS is defined as the condition of which CD4 T-cells fall to critically low level and individuals develop opportunistic infections such as CMV retinitis, *Mycobacterium avium* infection, *Pneumocystis carinii* pneumonia, HIV associated malignancies or other AIDS defining illness.



Answer

(1.) Fever, swollen lymph nodes, weight loss, malaise.
(3.) Seroconversion (ELISA/WESTERN blot positive)
(4.) CTL response to control plasma viral load
(5.) Rapid progression to AIDS, within two years
(6.) Slow progression to AIDS, greater than five years.
(2.) AIDS-defining illnesses (*e.g.* PCP, disseminated Mycobacterium infection, CMV retinitis, cryptosporidiosis)

The answer for question 10 is - d. The most cost effective way to diagnose HIV infection in adults is to test for presence of HIV antibodies to the various HIV proteins. The ELISA method is inexpensive and has a high sensitivity to detect the presence of HIV antibodies in sera. The Western blot assay is used as a confirmation assay and has higher specificity because it tests for antibodies to specific viral proteins. The combination of a positive HIV ELISA and Western blot indicates that an individual has been infected with HIV virus and hence mounted an antibody response to the virus. Some patients in HIV vaccine trials also develop positive ELISA and Western Blot tests. It takes between 2 weeks to 6 months following initial infection before HIV antibodies are detectable in the serum (see Figure 5). As a result there is a "window" of time when an infected individual has high levels of virus in the blood but has not yet have developed anti-HIV antibodies. During this time the ELISA and Western blot will be negative even though the patient is infected. **(b and c are therefore incorrect)** In children, transplacentally acquired maternal antibody persists in the child for up to a year. As a result even uninfected infants born to HIV-infected mothers will have a positive HIV ELISA and Western blot results due to maternal IgG. Thus, the HIV ELISA and Western blot tests are not good tests for the diagnosis of HIV infection in infants.

Patient IV: Baby Bambino

You have used your much needed vacation to join the organization "Doctors Without Borders" to serve as a volunteer to treat refugees involved in a Civil War that is ongoing in a developing nation. One of the families that you see in a refugee camp is a young pregnant mother who has a 14 month old infant who appears to be severely ill. The child has oral candidiasis, a markedly enlarged liver and spleen, and his neurologic exam shows developmental delay, hyperreflexia, and a small head circumference. In addition, he has a very fast heart rate and signs of congestive heart failure. The mother appears to be approximately 6 months pregnant with another child.

1. What are the likely causes of this child's symptoms?

   The most likely cause of this child's symptoms is AIDS as a result of HIV infection. Other causes could include malnutrition or other congenital infections such as SMU, Syphilis, or toxoplasmosis. The child shows clinical evidence of involvement of the immune system (oral candidiasis) with hepatosplenomegaly, HIV associated heart failure (high heart rate), and HIV encephalopathy(spastic diplegia, microcephaly, and developmental delay).

2. What would you tell this mother about her child's diagnosis?

   You suspect this child has AIDS, however, you do not have the resources to confirm the diagnosis. It is highly likely that this child will die within the next few months due to the complications of HIV infection. It is unlikely that highly active antiretroviral therapy will be available to this mother and even if instituted the chances the child improving and having a long term good outcome are small.

3. Are there any ways to protect this mother's unborn baby?

   There is now evidence that short-term therapy with antiretroviral agents where the mother receives even one dose of antiretroviral therapy and the baby receives another dose may be highly effective in preventing perinatal transmission in developing countries. However, there is still a great cost of screening for HIV infection among pregnant women in developing countries and also the problem of transmission through breast feeding. Unless there is alternative means of nutrition for infants in the developing world it is highly likely that HIV infection will continue even if strategies using antiretroviral therapy in the perinatal period are implemented.

Ethical Issues/Attitudes

A government representative is with you and asks if there are any effective ways of preventing maternal HIV transmission in developing countries where access to combination antiretroviral therapy and intravenous treatments are not practical. What would you advise this developing nation to do to reduce pediatric HIV infection?

Developing countries could use four separate strategies to reduce perinatal transmission. Without using excessive resources, these would include:

1. A program of HIV screening for pregnant women using inexpensive, saliva based assays to detect women who have positive HIV antibodies.

2. A program of education to prevent transmission through sexual contact and also to education women as to how HIV is transmitted from mother to child.

3. The use of inexpensive short term courses of antiretroviral treatments in which the mother and baby receive a single dose of medication.

4. The availability of clean water and powdered infant formulas as an alternative to breast feeding.

The use of resources to treat infected children is probably not practical in developing countries. The children would need to take daily antiretroviral therapy for life. It is estimated that the life long costs of treating an HIV infected child is over one million dollars and there are currently millions of children infected in developing countries. This treatment strategy would be difficult.

The best strategy for developing countries is to prevent infection. The use of antiretroviral therapy is the most practical way until a vaccine is developed.

POST TEST

1. Assuming no major breakthroughs in treatment or prevention, which one of the following groups is most likely to have the lowest number of AIDS cases in 2010 in the U.S.?

(A) homosexual or bisexual men
(B) IV drug abusers
(C) heterosexual males
(D) heterosexual females
(E) children

2. Which of the following statements is true about health workers who suffer accidental needle sticks with needles that have been used on HIV infected patients?

(A) They are certain to be infected.
(B) Their risk is about the same as that of an IV drug abuser (IVDA) sharing a needle one time.
(C) Their risk is less than that of an IVDA but more than that of an episode of receptive anal intercourse with an infected partner.
(D) Their risk is less than anal intercourse, but comparable to one episode of vaginal intercourse with an infected partner.
(E) They are at no risk.

3. A patient has just discovered that her sex partner is HIV seropositive. She is on the Pill so they have not been using condoms. They have had sex about 10 times. She left him this week. Her blood test is negative and she has never had an STD. Which <u>one</u> of the following statements is true?

(A) She is not infected with HIV and need not be tested again.
(B) She definitely needs to be tested again because she is certainly infected with HIV
(C) She is probably infected with HIV and should be tested again to be sure.
(D) She needs to be tested again in 6 months and if still seronegative, she is definitely uninfected.
(E) She needs to be tested again in 6 months and if seronegative, she is probably uninfected.

4. Which <u>one</u> of the following statements is <u>false</u> about HIV?

(A) HIV *env* gene codes for the surface antigens, gp41 and gp120.
(B) HIV has a unique *pol* gene product, reverse transcriptase, that can make DNA copies of RNA.
(C) HIV can mutate its envelop protein gp120 so as to change its antigenic character.
(D) HIV can be either HIV-1 or HIV-2.
(E) HIV protease inactivates many of the drugs used for treatment of HIV.

5. From the point of view of managing an HIV infected patient, the least important concept is realizing that:

(A) the amount of virus in the blood predicts the clinical outcome
(B) the virus can be spread by sex or by sharing IV needles.
(C) the patient is at risk for a series of opportunistic infections depending on the degree of immunodeficiency
(D) antiviral viral therapy can prolong life and maintain health
(E) gay men and IV drug abusers are currently the two most at risk groups.

6. Which <u>one</u> of the following statements is <u>false</u> about AZT?

(A) AZT given within minutes or hours of a needle stick may prevent HIV infection.
(B) AZT inhibits DNA synthesis in HIV infected cells.
(C) AZT inhibits DNA synthesis in normal cells like neutrophils.
(D) AZT can not cure AIDS infection.
(E) AZT treatment leads to significant cost savings.

7. On your last day in the ER, you see a 26 year old man with one week of fever, sore throat, malaise, and headache. You had seen him on your first day 4 weeks ago and treated him for gonococcal urethritis, which he had acquired 3 days previously, after his first sexual intercourse with a new partner. You review his records and his HIV test was negative at that time. On exam, his temperature is 39°C, he has a few shallow ulcers on his soft palate, a maculopapular rash on his chest, and diffuse adenopathy. Assuming he is infected with HIV-1, which of the following test results are most likely?

	HIV ELISA	HIV Western blot	Quantitative HIV RNA
(A)	Negative	Negative	Undetectable
(B)	Negative	Negative	1,200,000
(C)	Negative	Positive	Undetectable
(D)	Positive	Negative	1,200,000
(E)	Positive	Positive	Undetectable

8. Which of the following vaccines would be contraindicated in an HIV-positive person?

(A) Influenza vaccine
(B) Live Variella Zoster vaccine
(C) Pneumovax (pneumococcal polysaccharide vaccine)
(D) Tetanus-diphtheria vaccine
(E) Inactivated polio vaccine

9. It is proving to be very difficult to develop a vaccine which can prevent HIV infection. Which <u>one</u> of the following is false?

(A) The gp120 varies from HIV isolate to HIV isolate.
(B) Cell associated HIV may infect without being exposed to antibody.
(C) Cell mediated immunity will not stop the initial infection by cell free virus.
(D) p24 protein varies from HIV isolate to HIV isolate.
(E) Some antibody can actually enhance HIV infection rather than prevent it.

10. A man has just tested positive for HIV. He is married and his wife is seronegative. They use condoms for vaginal intercourse, but want to know about relative risks of other sexual practices. Without barrier protection, which of the following carries the greatest risk of transmission?

(A) fellatio
(B) cunnilingus
(C) mutual masturbation without vaginal penetration
(D) mutual masturbation with vaginal penetration by finger
(E) anilingus

POST TEST ANSWER SHEET

1. **Assuming no major breakthroughs in treatment or prevention, which one of the following groups is most likely to have the lowest number of AIDS cases in 2010 in the U.S.?**

   Children (**E**) is correct. Antiviral therapy given to pregnant women almost completely prevents HIV transmission.

2. **Which of the following statements is true about health workers who suffer accidental needle sticks with needles that have been used on HIV infected patients?**
   D is correct. The risk is less than 0.4%.
   Use of combination antiretroviral therapy may reduce this risk further.

3. **A patient has just discovered that her sex partner is HIV seropositive. She is on the Pill so they have not been using condoms. They have had sex ~ 10 times. She left him this week. Her blood test is negative and she has never had an STD. Which one of the following statements is true?**
   She may be in the "window" between infection and seroconversion, so she should be tested again. Almost all infected patients seroconvert in 6 months, but not all. Therefore **E** is correct.

4. **Which one of the following statements is false about the AIDS virus?**

   E is false. The protease cleaves the HIV long protein precurors into active proteins.

5. **From the point of view of caring for an HIV infected patient, the most important concept is realizing that:**

   Although all of the answers are correct, **E** is the least relevant in treating or counseling HIV patients.

6. **Which one of the following statements is false about AZT?**

   At this time it is not clear whether early initiation of therapy will lead to any long-term cost savings; the answer is **E**.

7. **On your last day in the ER, you see a 26 year old man with one week of fever, sore throat, malaise, and headache. You had seen him on your first day 4 weeks ago and treated him for gonococcal urethritis, which he had acquired 3 days previously, after his first sexual intercourse with a new partner. You review his records and his HIV test was negative at that time. On exam, his temperature is 39°C, he has a few shallow ulcers on his soft palate, a maculopapular rash on his chest, and diffuse adenopathy. Which of the following test results are most likely?**
   He likely has acute HIV syndrome, related to his unprotected contact about 4 weeks ago. Patients during the acute syndrome have very high levels of virus (usually over one million copies/ml) and have not yet developed any detectable immune response. Thus, his antibody tests are generally negative. Answer **B** is the best choice.

8. Which one of the following statements is true about prophylaxis?

Answer **B** is contraindicated because HIV-positive individuals should not receive live virus vaccines because their impaired cell-mediated immunity could lead to dissemination of the vaccine virus.

9. It is proving to be very difficult to develop a vaccine which can prevent HIV infection. Which one of the following is false?

D is false. Group antigens (*gag*) such as p24 do not vary the way *env* antigens do.

10. When there is no cure, prevention is the only rational choice. Which one of the following statements is false?

Because the HIV virus is in highest concentration in the blood and semen, fellatio (**A**) carries the highest risk.